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Review

Mouse models for liver cancer

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ABSTRACT

Hepatocellular carcinoma (HCC), the most common form of primary liver cancer is the third leading cause of cancer-related cell death in human and the fifth in women worldwide. The incidence of HCC is increasing despite progress in identifying risk factors, understanding disease etiology and developing anti-viral strategies. Therapeutic options are limited and survival after diagnosis is poor. Therefore, better preventive, diagnostic and therapeutic tools are urgently needed, in particular given the increased contribution from systemic metabolic disease to HCC incidence worldwide. In the last three decades, technological advances have facilitated the generation of genetically engineered mouse models (GEMMs) to mimic the alterations frequently observed in human cancers or to conduct intervention studies and assess the relevance of candidate gene networks in tumor establishment, progression and maintenance. Because these studies allow molecular and cellular manipulations impossible to perform in patients, GEMMs have improved our understanding of this complex disease and represent a source of great potential for mechanism-based therapy development. In this review, we provide an overview of the current state of HCC modeling in the mouse, highlighting successes, current challenges and future opportunities.

1. Introduction

The World Health Organisation estimates that in 2008, liver cancer accounted for almost 700 000 deaths worldwide, half of these in China and more than 60 000 within Europe. It is the 6th most common cancer type and the third most common cause of death from cancer worldwide with, at the moment, the highest incidence in Asia and sub-Saharan Africa. Primary liver cancer consists of several histologically different malignancies, such as cholangiocarcinoma, hepatoblastoma and hemangiosarcoma, although hepatocellular carcinoma (HCC) is by far the most common type, accounting for 70–80% of cases. Chronic hepatitis virus infections (HBV or HCV) and to a lesser extent, aflatoxin B-contaminated dietary intake are the major risk factors in areas of high HCC incidence, while chronic alcohol consumption, obesity-related fatty liver diseases, autoimmune hepatitis and genetically determined disorders, such as hemochromatosis, are important contributors, in particular in areas with lower incidence, such as Europe (Ferlay et al., 2010; Nordenstedt et al., 2012).

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As chronic HBV or HCV infections currently account for more than 80% of HCC, the best strategy to prevent HCC is to eradicate viral infections. A vaccine against HBV has been developed in 1982 and is routinely used in many countries. Vaccination has reduced persistent HBV infections and led to marked reduction in hepatitis B-related liver cancer (Romano et al., 2011). However, the millions of adults, who were infected before universal vaccination or that cannot afford it, are still at risk of developing HCC and the emergence of vaccine-resistant hepatitis B surface antigen mutants is a serious concern. Hepatitis C-associated cirrhosis is the leading cause of liver transplantation and despite encouraging results, no vaccine can currently protect against HCV infection (Feinstone et al., 2012). Fortunately, a treatment is available and effective in 50–80% of patients with persistent HCV infection, and better treatments are in sight (Dore, 2012). However, therapeutic options remain costly and patients with advanced liver pathologies will continue to require expensive disease management.

While the incidence of HCC in the areas endemic for viral infections has started to decline, its increase in developed countries is an important health concern. Different studies identify chronic alcohol ingestion, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), NASH-related cryptogenic cirrhosis and even diabetes as relevant contributors for increased HCC incidence. NAFLD is the hepatic manifestation of the metabolic syndrome and the epidemiology of NAFLD mirrors the increased prevalence of obesity and diabetes. NAFLD has become the most common liver disorder in industrialized countries, affecting up to 30% of the adult population (Lazo and Clark, 2008). Given the increase in the prevalence of overweight, obesity and type 2 diabetes, the incidence of metabolic disease-related HCC is expected to rise, further increasing the burden of liver diseases in years to come (Baffy et al., 2012). Understanding the cellular and molecular mechanisms leading to HCC, and most importantly those which are connected to systemic/metabolic influences has therefore become an urgent and imperative issue. Without this knowledge, developing efficient preventive, diagnostic and therapeutic countermeasures is bound to fail.

Establishing animal models for HCC is essential for both basic and translational studies. Several rodent models have been used over the years to study HCC pathogenesis. The laboratory mouse is one of the best experimental systems, owing to the physiologic, molecular and genetic similarities to humans, its breeding capacity, short lifespan and the unlimited options offered by genetic engineering. More recently, an entirely sequenced genome, the possible use of defined genetic, but also environmental conditions, the establishment of non-profit repositories and resource centers worldwide and the promising perspectives of national or transnational initiatives, for instance the International Knockout Mouse Consortium (IKMC) or the NCI's Mouse Models of Human Cancers Consortium (MMHC) have increased the range of potential benefits for using mouse models (GEMMs) in cancer research. In this review, we provide an overview of HCC modeling in the mouse, highlighting how simple and more sophisticated models have helped unraveling important aspects of disease development (Table 1). The utility of mouse models to establish and dissect HCC complexity and experimentally test clinically relevant hypotheses will be illustrated by selected examples and the challenges and future opportunities will be discussed. We also refer to excellent recent reviews, since by no means are we covering all aspects of HCC development.

Table 1 – Mouse models to study HCC development.

	Properties	Latency	Notes
Chemical			
DEN/Phenobarbital DEN (single injection)	Genotoxic	5–10 m	When DEN is injected to adults promotion is needed, used in combination with genetic/dietary/environmental models
Aflatoxin	Genotoxic	>22 m	Often combined with genetic models
CDE diet, TAA, CCl4, peroxisome proliferators etc.	Associated with steatohepatitis, fibrosis, etc.	>12 m	Variability due to different experimental protocols, used for context-specific modeling. Often combined with DEN or genetic models
GEMMs			
HBV-derived (sAg, HBx)	ER stress,focal necrosis, proliferation	12–24 m	Several lines/backgrounds with different penetrance/latency
HCV-derived (Core)	Steatosis	12–24 m	Several lines/backgrounds with different penetrance/latency
Mdr2 knock-out	Cholangitis	>12 m	Strong inflammatory component, strain dependent
Mosaic GEMMs			
Somatic gene/molecules delivery: Virus-based, RCAs/TVA, Hydrodynamic	Fast, cost-effective	Few weeks	Can be combined with GEMMs, suitable for imaging
Implantation models: p53KO; mycTg hepatoblasts	Fast, cost-effective	Few weeks	Suitable for imaging and large-scale screens

More examples and details can be found in Newell et al., 2008; Li et al., 2011.